**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| CELGENE CORPORATION,<br><br>Plaintiff,<br>v.<br><br>NATCO PHARMA LIMITED,<br>ARROW INTERNATIONAL LIMITED,<br>and WATSON LABORATORIES, INC.<br><br>Defendants. | : | Honorable Susan D. Wigenton, U.S.D.J.<br><br>Civil Action No. 10 CV 5197 (SDW) (MCA)<br><br>**Electronically Filed** |
| NATCO PHARMA LIMITED,<br>ARROW INTERNATIONAL LIMITED,<br>and WATSON LABORATORIES, INC.<br><br>Counterclaim Plaintiffs,<br><br>v.<br><br>CELGENE CORPORATION,<br><br>Counterclaim Defendant. | : | |

# DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF

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## I. INTRODUCTION

The drug at issue in this case is called lenalidomide. Celgene sells it under the trade name Revlimid® to treat certain types of a blood cancers—multiple myeloma and mantle cell lymphoma—as well as certain types of another blood disorder called myelodysplastic syndrome. Natco filed an ANDA seeking approval to commercially market a generic lenalidomide drug product prior to expiration of certain patents covering the drug, its formulation, and methods of using it.

The claim construction issues in this case involve four sets of patents. The first patent family covers four patents (the "Polymorph Patents") relating to different solid forms of lenalidomide – the active ingredient at issue in this case. The claims are directed to crystal forms of lenalidomide that are defined in the patent specification as "Form A" and "Form B." Natco's proposed construction remains faithful to the ordinary understanding of the terms at issue as modified by the inventors themselves. Celgene, however, proposes a litigation-driven construction that ignores the inventors' own statements and tries to expand the relevant terms beyond the specific Form A and Form B lenalidomide described in the specification. In other instances, Celgene proposes no construction at all, although the terms are in dispute, technical in nature, and non-construction gives rise to issues of non-enablement, lack of written description, and/or indefiniteness. The Court should reject Celgene's proposals for at least these reasons.

The second patent family (the "Pharmaceutical Patents") relates to methods of treating certain conditions using lenalidomide or similar substances. Natco's proposed constructions stay faithful to the intrinsic evidence and scientific principles. By contrast, Celgene's proposals ignore that evidence and are therefore incorrect.

The third and fourth patent families each cover one patent (the "Multiple Myeloma Patent" and the "MDS Patent") relating to methods of treating multiple myeloma and

myelodysplastic syndrome by administering lenalidomide. The disputed claim terms relate to the required "cyclical" dosing regimen. Natco's proposed constructions are faithful to the meanings of these terms as defined and consistently applied in the intrinsic record. Despite the unambiguous specification definitions of these terms, Celgene asserts that these technical terms do not require construction. The Court should reject Celgene's litigation-driven attempt to supplant the intrinsic record, and adopt Natco's construction instead.

## II. CLAIM CONSTRUCTION PRINCIPLES

The claim construction process is a matter of law for the Court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). However, just because one party seeks construction does not mean the Court must indulge that request. The Federal Circuit has stated that courts must instead "indulge a 'heavy presumption' that a claim term carries its ordinary and customary meaning," and must not deviate from that "[i]n the absence of an express intent to impart a novel meaning to claim terms." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002).

### A. Claims Must Be Interpreted In Light Of Their Own Language

As part of the inquiry into whether to jettison the plain and ordinary meaning of a term, the Federal Circuit reaffirmed in *Phillips v. AWH Corporation* the "bedrock principle" that "the claims of a patent define the invention to which the patentee is entitled the right to exclude." 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotations omitted). Accordingly, claim construction starts with the words of the claims themselves, which "are generally given their ordinary and customary meaning" and which can "provide substantial guidance as to the meaning of particular claim terms." *Id.* at 1312, 1314.

### B. The Specification And File History Inform Claim Construction

Claim terms should also be interpreted "in view of the specification, of which they are a part." *Id.* at 1315 (internal quotations omitted). One important reason for consulting the specification is to determine whether "the patentee, acting as his or her own lexicographer, has clearly set forth a definition of the term different from its ordinary and customary meaning," *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1091 (Fed. Cir. 2003), or "by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope," *Teleflex*, 299 F.3d at 1324.

Courts also may consider a patent's prosecution history when construing its claims. That file is "the complete record of the proceedings before the PTO" when the patentee was applying for the patent. *Phillips*, 415 F.3d at 1317. "[L]ike the specification, the prosecution history was created by the patentee in attempting to explain and obtain the patent." *Id.* The prosecution history can thus demonstrate "how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution . . . ." *Id.*

### C. Extrinsic Evidence Is Less Relevant Than The Intrinsic Record

Finally, courts may also consider "extrinsic evidence," which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Id.* at 1317 (internal quotations omitted). "[W]hile extrinsic evidence can shed useful light on the relevant art, . . . it is less significant than the intrinsic record in determining the legally operative meaning of claim language." *Id.* (internal quotations omitted).

## III. DISPUTED TERMS OF THE POLYMORPH PATENTS

Four of the patents-in-suit—U.S. Patent Nos. 7,465,800 (the "'800 patent"), 7,977,357 (the "'357 patent"), 8,193,219 (the "'219 patent"), and 8,431,598 (the "'598 patent")

(collectively, the "Polymorph Patents")—purport to cover particular solid forms of lenalidomide. Lenalidomide, like many other compounds, can exist in different crystal forms called "polymorphs." Each polymorph contains the same lenalidomide molecules, but arranges those molecules in different configurations that can have different characteristics. As the Polymorph Patent specification states, "[i]n the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions." (Ex. B, '800 patent, col.1 ll.28-31.)[1]

**A. "3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione"[2]**

The asserted Polymorph Patent claims require crystalline "3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione." The parties agree that this term generally describes the lenalidomide compound. The dispute arises from the fact that the specification limits this term to lenalidomide that is "prepared according to the methods described in U.S. Patent Nos. 6,281,230 and 5,635,517," which are two other patents asserted against Natco. (*See* Ex. B, '800 patent, col.4, ll.66-67.) This dispute is relevant because Natco's lenalidomide is not made by any of those methods, and it therefore does not infringe claims limited to those methods. The parties' constructions are as follows:

[1] All references herein to "Ex. __" refer to exhibits attached to the accompanying Declaration of Melissa Steedle Bogad ("Bogad Declaration"), submitted herewith.

[2] A chart showing where each disputed term appears in exemplary claims, and how it is used in those claims, is attached to the Bogad Declaration as Exhibit A.

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| 3-(4-amino-l-oxo-l,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione<br><br>(*'800 patent, claims 1, 10; '357 patent, claims 1-15; '219 patent, claims 1, 3-5, 7-8, 11-12, 15; '598 patent, claims 1-8, 10-13, 17-23*) | Lenalidomide, prepared according to the methods described in U.S. Patent Nos. 6,281,230 and 5,635,517 | No construction required |

The principle that controls this construction issue is the Federal Circuit's statement that the patentee's definition of a term controls when the patentee, "acting as his own lexicographer, has clearly set forth a definition of the term different from its ordinary and customary meaning." *ACTV*, 346 F.3d at 1091. Here, the patentee did just that.

The invention claimed in the '800 patent "relates to polymorphic forms of 3-(4-amino-l-oxo-l,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione," and "methods of making the polymorphic forms . . . ." (Ex. B, col.1, ll.12-15.) The specification then goes on to describe the structure of lenalidomide. (*Id*. at col.4, ll.55-62.) Importantly, the inventors then teach the person of ordinary skill in the art ("POSA") how to make the claimed invention, stating expressly that lenalidomide "can be prepared according to the methods described in U.S. Pat. Nos. 6,281,230 and 5,635,517, the entireties of which are incorporated herein by reference." (*Id*. at col.4, l.66 – col.5, l.1.) The specification then proceeds to detail how, from the lenalidomide prepared by the processes denoted in the '230 and '517 patents, various polymorphic forms of lenalidomide may be obtained, as claimed in the '800 patent. (*Id*. at col.5, ll.13-32.)

A POSA would not have read the term "3-(4-amino-l-oxo-l,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione" in a vacuum, but instead within the context of the specification disclosure in determining its meaning. *See Combined Sys., Inc. v. Def. Tech. Corp. of Am.*, 350 F.3d 1207 (Fed. Cir. 2003). Thus, contrary to Celgene's position, a POSA would not selectively focus on

the chemical name of lenalidomide to the exclusion of the remaining specification language regarding how to make the compound and claimed polymorphs.

The language regarding how to make lenalidomide is especially relevant because there is nothing in the intrinsic record to suggest that the processes recited in U.S. Pat. Nos. 6,281,230 and 5,635,517 are merely representative or illustrative of methods by which lenalidomide can be made. Rather, by failing to disclose or suggest even a single alternative process for making lenalidomide, the intrinsic record clearly shows that the processes disclosed in the '517 and '230 patents are the *only* methods by which the patentee contemplated making the compound. Based on the unequivocal limiting definition of "3-(4-amino-l-oxo-l,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione" as the compound made by the methods of two prior patents, Natco's proposed construction reflecting that limiting definition is the correct one. Celgene may not now, almost five years after the patent issued, ignore those statements and argue that the compound should be entitled to a broader scope than was identified to the PTO during prosecution.

**B. "Hemihydrate"**

All asserted claims of the '800 patent expressly require a "hemihydrate" of a certain crystalline form of lenalidomide. The parties' constructions of "hemihydrate" are as follows:

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| Hemihydrate<br><br>(*'800 patent, claims 1-14*) | A solid crystalline form of lenalidomide containing one water molecule for every two molecules of 3-(4-amino-l-oxo-l,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, formally associated with one another within the unit cell in the solid crystalline structure, and which crystal form is specifically identified in the '800 patent as the Form B polymorphic form, and demonstrated in TGA, Karl Fischer analysis, powder X-ray diffraction patterns, IR spectra, and/or DSC analysis, as distinguishable from other polymorphs, such as the anhydrous form | A hydrate containing approximately half a mole of water to one mole of the compound forming the hydrate |

### 1. "Hemihydrate" Is Not A Term Of Approximation

#### a. Natco's Construction Is Consistent With The Intrinsic Record

The parties dispute whether the term "hemihydrate" refers to an exact 1:2 ratio of water to lenalidomide (Natco's proposal), or whether the term is intended as an approximation (Celgene's proposal). This issue has already been decided by the Federal Circuit, which defined hemihydrate just as Natco proposes. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339 (Fed. Cir. 2005) (construing the term "crystalline paroxetine hydrochloride hemihydrate" as "a crystal form of paroxetine hydrochloride that contains ***one molecule of bound water for every two molecules*** of paroxetine hydrochloride") (emphasis added). This case is no different because there is nothing in the specification suggesting that Celgene intended to alter the ordinary definition of "hemihydrate," as would have been understood by a POSA. Thus, Natco's construction is the correct one.

Natco's construction—requiring a hemihydrate to occur in a fixed 1:2 ratio rather than as a term of approximation—is fully supported by the language of claim 1. (*See, e.g.*, Ex. C,

Webster's New Collegiate Dictionary 564 (9th ed. 1991) (defining "hemihydrate" as "a hydrate containing half a mole of water to one mole of the compound forming the hydrate," equivalent to a 1:2 ratio); Ex. D, Remington: The Science and Practice of Pharmacy, 175 (20th ed. 2000) ("During the process of crystallization, some compounds have a tendency to trap a *fixed* molar ratio of solvent molecules in the crystalline (solid) state. . . . When water is used as the solvent, hydrates may be formed.") (emphasis added); Ex. E, Webster's Collegiate Dictionary 540 (10th ed. 2003) (defining "hemihydrate" as "a hydrate . . . containing half a mole of water to one mole of the compound forming the hydrate.") (cited by Celgene in support of its construction); Ex. F, Webster's Collegiate Dictionary 579 (11th ed. 2004) (defining "hemihydrate" as "a hydrate . . . containing half a mole of water to one mole of the compound forming the hydrate.") (cited by Celgene in support of its construction).

This construction makes perfect sense when one considers the scientific background. When the ratio of water molecules to crystal molecules can be expressed as an exact common fraction or integer, the crystal is labeled with a term like hemihydrate, or "monohydrate" when the ratio is 1:1. (Second Decl. of Mark D. Hollingsworth, Ph.D. ("Hollingsworth Decl.") ¶ 19.) But when the ratios cannot be expressed as common fractions or integers—like Celgene's construction allows—there is no common hydration label for the crystal. It is simply referred to by the ratio itself, *e.g.*, a crystal with a hydration ratio of .46:1 or .59:1. (*Id.* at ¶ 20.)

Celgene's own expert, Dr. Stephen Byrn, recognized in a textbook he authored that hydrates that can be reported as simple ratios are not terms of approximation, but instead refer to an exact simple ratio. Specifically, in a section containing definitions of terms used in his textbook, Dr. Byrn defines "monohydrate" (what Natco contends is a one-to-one ratio of water to the compound) as "[a] crystal form containing one mole of water per mole of compound." (Ex.

G, Stephen R. Bryn et al., Solid-State Chemistry of Drugs 512, 515 (2d ed. 1999).) [redacted] Celgene's proposed construction is contrary to these principles and the ordinary meaning of "hemihydrate" to the extent it seeks to broaden this term to anything beyond an exact 1:2 ratio of water to lenalidomide. (Hollingsworth Decl. ¶¶ 19, 22.)

**2. "Hemihydrate" Refers To The Form B Polymorph**

The parties also dispute whether the claimed hemihydrate is limited to the crystalline form known as "Form B." Natco's construction adopts that position based on the specification's clear definition of "hemihydrate" as Form B lenalidomide, as well as Celgene's unambiguous disavowal of crystalline forms other than Form B.

**a. The Specification Shows That "Hemihydrate" Refers To Form B Lenalidomide**

The patent specification is replete with references to the "hemihydrate" being Form B lenalidomide. In fact, it is the only hemihydrate identified: "Intrinsic dissolution experiments were conducted on Form A (anhydrous), ***Form B (hemihydrate)*** and Form E (dihydrate) of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione." (Ex. B, '800 patent, col.17, ll.37-40 (emphasis added)); "***Form B is a hemihydrated***, crystalline material that can be obtained from various solvent systems." (*Id*. at col.5, ll.39-40 (emphasis added); "In sum, ***Form B is a hemihydrated***, crystalline solid . . . ." (*Id*. at col.7, l.31 (emphasis added)).) Then, upon full analysis and characterization of the compounds, the specification again concludes that the hemihydrate is the Form B polymorph:

> Form B typically loses about 3.1% volatiles up to about 175° C. (per approximately 0.46 moles of water). Comparison of the IR

> spectrum of the volatiles with that of water indicates that they are water (See FIG. 10). ***Calculations from TGA data indicate that Form B is a hemihydrate. Karl Fischer water analysis also supports this conclusion***.

(*Id*. at col.6, l.67 – col.7, l.6 (emphasis added).)

Because no *other* so-called "hemihydrate" is identified anywhere in the specification, the term "hemihydrate" in the context of the '800 patent must be construed to cover only the Form B polymorph, as Natco proposes. This conclusion is mandated by the Federal Circuit's opinion in *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). In that case, the court construed the broad term "crystalline" to mean a particular type of crystal known as "Crystal A." *Id*. at 1289. It did so in part because Crystal A was the only embodiment described in the specification, the specification showed seven particular distinguishing X-ray powder diffraction peaks associated with Crystal A, and the patent offered no suggestion that the recited processes could produce non-Crystal A compounds, even though other crystalline forms were known. *Id.*

The evidence in this case is even more compelling in favor of Natco's proposal not only because the specification expressly recognizes Form B as the desired polymorph, but also because the specification offers no suggestion that the hemihydrate can exist as any polymorph other than Form B. (*See* Ex. B, '800 patent, col.12, ll.31-32.) The specification also expressly distinguishes all other disclosed polymorphic forms as having hydration states other than the hemihydrate: "Form A is an unsolvated, crystalline material . . . ."; "Form C is a hemisolvated, crystalline material . . . ."; "Form D is a crystalline, solvated polymorph . . . ."; "Form E is a dehydrated, crystalline material."; "Form F is an unsolvated, crystalline material . . . ."; "Form G is an unsolvated, crystalline material . . . ." (*Id.* at col.5, ll.35, 39, 42-43, 47, 50-51, 53-54, & 57-58.)

Natco's proposed construction is also appropriate in the context of dependent claims 2-14. *See Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) ("[A] claim term should be construed consistently with its appearance in other places in the same claim or in other claims of the same patent."). Claims 2-14 further define the claimed hemihydrate in terms of its X-ray powder diffraction ("XRPD") pattern, differential scanning calorimetry ("DSC") thermograms, and infra-red ("IR") spectra and Raman spectra, all of which correspond to attributes that the specification specifically identifies and associates with only the Form B polymorph. (Ex. B, '800 patent, col.6, l.54 – col.7, l.35.)

Notably, *all* the intrinsic evidence cited by Celgene in support of its construction also fully supports Natco's position that the claimed hemihydrate refers to the Form B polymorph. (*See, e.g.*, *id.* at col.5, ll.36-40; col.6, l.53 – col.7, l.35; col.12, ll.31-36; col.22, ll.40-43.) Indeed, each of the cited disclosures describes, to the exclusion of any other polymorph, the Form B polymorph and its analytical attributes.

**b. Celgene Disavowed Claim Scope Covering Other Polymorphs**

Celgene's conduct during prosecution also resolves any remaining question about whether "hemihydrate" includes anything other than the Form B polymorph.

The original claims of the '800 patent were not limited to a hemihydrate, let alone the Form B polymorph. Instead, they covered several polymorphs of undefined water content. (Ex. I, '800 patent file history, Original Application at 32-35.) This breadth was specifically noted by the examiner when the PTO requested that Celgene elect to pursue only one group of claims. In particular, the examiner noted that "each crystalline form of [lenalidomide] is a 'product' with different chemical identi[t]y and physical characteristic[s], which can be made and sold separately, thus, support separate patent[s]." (Ex. J, '800 patent file history, 6/22/07 Office Action at 3.) Celgene responded by electing the group of claims specifically drawn to the Form

B polymorph and further requested that other groups directed to the same crystalline form (Form B), or those containing a mixture of Form B and Form E, be examined together with the elected claims. (*See* Ex. K, '800 patent file history, 7/23/07 Amendment at 9-10.) In support of claims directed to the "same crystalline form," Celgene identified disclosures in the original specification which described "Form B" and its XRPD pattern, as well as other identifying tests including solution proton NMR, IR, Raman, DSC, TGA and Karl Fischer analysis. Each of these tests further identified Form B as a "hemihydrate." (Ex. I, '800 patent file history, Original Application at 9, ll.5-19.)

The examiner acknowledged Celgene's election but refused to examine claims directed to any mixture with the Form B claims. (Ex. L, '800 patent file history, 10/10/07 Office Action at 2.) As the examiner noted, "multiple forms do not exist together and mixtures are not considered to be the same as each individual crystalline form since each mixture must be obtained under specific condition[s]." (*Id.*) Accordingly, the examiner found inappropriate any claim that a mixture of polymorphs could be the same as a single polymorph. Thus, it is clear that, at the very least, "hemihydrate" in the claim must refer to a single polymorph.

In the same Office Action, the examiner also rejected the claims as being indefinite and failing to meet the written description requirement. (*Id.* at 2-3.) The examiner specifically "recommended that the chemical identity of the claimed product be explicitly employed since it is understood in the art that polymorphs of a compound all have the *same chemical and molecular composition.* Any molecular composition which is *different* is a different product and 'there should never be any doubt in this century about the chemical identify [sic] of a material.'" (*Id.* at 2 (emphasis in original) (citation omitted).)

In response, Celgene cancelled all pending claims directed to a crystalline form without reference to a specific product and added claims directed to "crystalline [lenalidomide] hemihydrate." (Ex. M, '800 patent file history, 1/9/08 Amendment at 2-3.) In support of this amendment, Celgene specifically identified sections of the original specification identifying the hemihydrate as "Form B." (*Id.* at 5.) It was only after this amendment that the examiner allowed the claims, noting in the process that:

> Applicants have ***limited*** the claims to the particular chemical product [crystalline] 3-(4-amino-l-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate. This product has been identified by chemical abstract (see Chen et al. CA 142:303619 recited on PTO-892 previously) and antecedent basis was found in the specification on page 9, lines 15-19.

(Ex. N, '800 patent file history, 4/30/08 Notice of Allowability at 2 (emphasis added); Ex. O, '800 patent file history, 11/3/08 Notice of Allowability at 2 (emphasis added).) The portions of the original specification referred to by the examiner at page 9, lines 15-19, specifically includes the language "Form B typically loses about 3.1% volatiles up to about 175 °C (per approximately 0.46 moles of water)." (Ex. I, '800 patent file history, Original Application at 9.)

Based on this clear prosecution history, in which Celgene was able to obtain claims to a "hemihydrate" only by responding to the examiner's requests for identification of a single compound with information about Form B, Natco's proposed construction is correct. By contrast, Celgene's attempts to broaden the scope of "hemihydrate" beyond Form B must fail because the specification discloses only one embodiment, the Form B polymorph, in connection with the hemihydrate. Celgene construction is similarly unavailing because it ignores the numerous arguments made during prosecution that limit "hemihydrate" to the Form B crystal.

### C. "Form A" Terms

The next dispute concerning the Polymorph Patents relates to certain terms in the '357 and '598 patents. The disputed terms and the parties' constructions are set forth below.

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| Form A<br><br>(*'357 patent, claims 1-14;'598 patent, claims 1-4*) | The lenalidomide crystal form described in the specification as Form A, having all of the characteristics assigned to Form A in the specification | A polymorphic form of 3-(4-amino-l-oxo-l,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione that can be distinguished from other forms |
| Unsolvated crystalline Form A of [lenalidomide]<br><br>(*'598 patent, claim 1*) | See above | No construction required |
| Unsolvated crystalline Form A of [lenalidomide] which has a differential scanning calorimetry thermogram having an endotherm at approximately 270 °C<br><br>(*'357 patent, claim 1*) | See above | No construction required |
| Unsolvated crystalline Form A of [lenalidomide] having a differential scanning calorimetry thermogram having an endotherm at approximately 270 °C<br><br>(*'598 patent, claim 1*) | See above | No construction required |

These claim terms expressly recite "Form A," and optionally recite an additional identifying characteristic that the specification associates exclusively with "Form A." (Ex. P, '357 patent, col.6, ll.50-51.) The parties agree that 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione refers to lenalidomide. The primary dispute concerns whether the terms should be construed to cover only the polymorph known as "Form A," with all the characteristics attributed to the Form A polymorph by the specification. This dispute is relevant because

Natco's proposed lenalidomide product does not contain a polymorphic form having all the characteristics assigned to Form A by the specification. Therefore, the accused products would not infringe claims requiring the "Form A" crystal if the Court adopts Natco's construction.

**1. "Form A"**

Not only does Natco's construction align with the specification, it also reflects Celgene's disavowal of other polymorphs during patent prosecution and is consistent with universally accepted principles of polymorph nomenclature and characterization. (Hollingsworth Decl.¶ 24, 26.)

**a. The Specification Supports Natco's Construction.**

The phrase "Form A" in the abstract has no established meaning. (Hollingsworth Decl. ¶ 24.) By contrast, a POSA would recognize it simply as a label given to a particular crystalline form that represents that crystalline form's characteristics as determined by various test methods, to distinguish it from all other crystalline forms. (*Id.*) The label assigned to a particular crystalline form (*e.g.* Form A, Form B, etc.) thus acts as a unique identifier representing the particular chemical and physical properties associated with that single crystalline form. (Hollingsworth Decl. ¶ 24.)

The Polymorph Patent specification thoroughly characterizes Form A on the basis of its observed characteristics.[3] And it is those characteristics that distinguish Form A from all of the other disclosed forms: B, C, D, E, F, G, and H. Under the label of "Form A," for example, the specification discloses crysalline lenalidomide having a specific XRPD pattern with characteristic peaks as shown in Fig. 1; specific IR and Raman spectra (Figs. 2 and 3); "[r]epresentative thermal characteristics" including TGA and DSC curves as shown in Fig. 4,

[3] These characteristics are determined using various measurement techniques known in the art including XRPD, IR, DSC, TGA, and Raman. (Ex. P, '357 patent, col.6, l.13 – col.10, l.30.).

and "[r]epresentative" moisture sorption and desorption data as depicted in Fig. 5 of the specification. (Ex. P, '357 patent, col.6, ll.13-54, Figs. 1-5.) These are unique among all of the disclosed crystalline forms and they describe only Form A. Thus, a POSA would understand "Form A" in these patents to mean the particular polymorph that has the various characteristics attributed to it by the specification. (Ex. P, '357 patent, col.6, ll.13-54.)

Celgene's proposed construction, by contrast, is circular and akin to no construction at all. First, a particular polymorphic form is, by definition, distinguishable from other polymorphic forms of the same compound. (Hollingsworth Decl. ¶ 26.) Celgene's construction therefore does nothing to elucidate the meaning of Form A as it is used in the claims. Indeed, Celgene's proposed construction applies equally for each of Forms A-H as disclosed in the Polymorph Patent specification, although they are each distinguishable from each other and all other polymorphic forms.

**b. The File History Further Supports Natco's Construction**

The prosecution history also supports Natco's construction. During prosecution of the '357 patent, Celgene originally pursued coverage of claims directed to unsolvated crystalline lenalidomide, without limitation to "Form A," but nevertheless reciting characteristics described by the specification as associated with the Form A crystal:

> 30. (Currently amended) ~~The~~ Unsolvated crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione ~~of claim 29~~, which has an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5 and 16 degrees 2θ.

(Ex. Q, '357 patent file history, 5/11/10 Preliminary Amendment at 2.) The examiner rejected these claims for lack of enablement, concluding that the specification at best only enabled unsolvated crystalline *Form A* lenalidomide: "the specification, while being enabling for [lenalidomide] Form A with a X-ray diffraction pattern of fig.1; does not reasonably provide

enablement for the claimed scope of 'unsolvated [lenalidomide] having approximately 8, 14.5, 16 degrees 2-theta or 7.9, 14.4, 15.8 degree 2-theta or 17.6, 20.6, 24.1, 26.0 degree 2-theta.'" (Ex. R, '357 patent file history, 6/18/10 Office Action at 4.)

In order to overcome the enablement rejection, Celgene expressly narrowed the claims to recite "Form A" lenalidomide. (Ex. S, '357 patent file history, 3/7/11 Interview Summary; Ex. T, '357 patent file history, 3/10/11 Supplemental Amendment and Response.) Natco's construction, which includes the data that Celgene ***assigned*** to Form A in the patent, is thus the correct construction.

Similarly, during prosecution of the '598 patent, Celgene identified specification disclosure describing the analytical characteristics of Form A, including XRPD, IR, DSC, TGA, Raman, and moisture sorption/desorption data in arguing that claims directed to "Form A" satisfied the enablement and written description requirements of 35 U.S.C. § 112. (Ex. U, '598 patent file history, 6/14/12 Office Action at 2-10.) In particular, Celgene identified Figures 1-5 of the originally filed specification as support that it had possession of the "Form A" claims at the time of filing. (Ex. V, '598 patent file history, 12/12/12 Amendment at 8 (citing page 8, line 7 to page 9 of the original specification).) Figures 1-5 describe various analytical characteristics of the Form A crystal including its XRPD, IR, Raman, DSC, TGA, and moisture sorption/desorption characteristics. Celgene also identified portions of the original specification describing Form A in terms of its analytical attributes, in arguing that the claimed inventions were sufficiently described and enabled. (*Id.*) Such arguments reflect Celgene's clear intent to define Form A by the combination of its analytical attributes as described in the specification.

The Court should reject Celgene's attempts to broaden the scope of "Form A" to cover lenalidomide forms other than Form A, as described by the specification, because such a

construction would effectively read out the "Form A" limitation. Notably, the specification does not disclose any embodiment in which the "Form A" crystal is described by only a subset of the characteristics associated with the Form A crystal. By contrast, the specification clearly describes the Form A crystal by reference to *all* its characteristics as measured using standard analytical techniques. Accordingly, any construction that allows "Form A" to cover crystalline forms that do not have all the characteristics assigned to Form A by the specification would render the "Form A" limitation meaningless. The Federal Circuit has repeatedly stated that a claim construction that gives meaning to all terms of the claim is favored over one that does not. *See Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005); *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 781 (Fed. Cir. 2010) ("[W]e construe claims with an eye toward giving effect to all of their terms . . . even if it renders the claims inoperable or invalid."). Therefore, the Court should adopt Natco's construction.

Celgene's construction of "Form A" also renders the claims insolubly ambiguous and therefore indefinite, for failing to provide a POSA with any reasonable guidance as to the metes and bounds of the claim. Celgene's construction therefore introduces ambiguity instead of clarity and leaves a POSA with the following questions:

- *How* must the lenalidomide be distinguishable from other forms in order to qualify as Form A?
- What analytical method(s) should be used to determine whether the crystal form is Form A (*e.g.* IR, XRPD, DSC, TGA, Raman, or some combination of these and/or other analytical techniques)?
- Which analytical attributes of Form A, as disclosed by the specification, should be satisfied in order for the crystal to qualify as Form A?

Finally, to the extent Celgene's construction allows for coverage of unsolvated crystalline lenalidomide forms other than Form A as described in the specification, this overbroad

construction should be rejected as rendering the claims invalid for lack of written description and/or enablement under 35 U.S.C. § 112, first paragraph. *See Modine Mfg. Co. v. U.S. Intern. Trade Comm'n*, 75 F.3d 1545, 1557 (Fed. Cir. 1996), *abrogated on other grounds by Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558 (Fed. Cir. 2000) ("When claims are amenable to more than one construction, they should when reasonably possible be interpreted so as to preserve their validity.") (internal citations omitted). While the patent specification discloses more than one unsolvated form of lenalidomide, it does not disclose or suggest any unsolvated crystalline form, other than Form A, that has the characteristics attributed by the specification to the Form A crystal, and as specifically recited in the '357 and '598 patent claims. (*See, e.g.*, Ex. P, '357 patent, claims 1-14; Ex. W, '598 patent, claim 1.) The specification also does not teach a POSA how to make any unsolvated crystalline form of lenalidomide, other than Form A, having the characteristics described in the specification and specifically recited in the '357 and '598 patent claims without undue experimentation. (Ex. P, '357 patent, claims 1-14; Ex. W, '598 patent, claim 1.)

Accordingly, even if Celgene's proposed construction may be appropriate in the abstract, which it is not, the Court should adopt Natco's construction because it clarifies the scope of the term as read in context. This result is mandated by the Federal Circuit and established principles of claim construction requiring that even if a claim term is amenable to more than one construction, the Court should interpret it to preserve its validity. *Modine Mfg. Co.*, 75 F.3d at 1557 (citing *Whittaker Corp. by its Technibilt Div. v. UNR Indus., Inc.*, 911 F.2d 709, 711 (Fed. Cir. 1990); *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984).)[4]

[4] If the Court nevertheless adopts Celgene's construction, Natco reserve the right to challenge the validity of the construed claims for failure to satisfy the written description, enablement and definiteness requirements of Section 112 of the Patent Act.

### 2. The Remaining "Form A" Terms In Dispute

The other three disputed terms recite "Form A" as part of a larger phrase requiring "an unsolvated crystalline" form and/or requiring a DSC thermogram having an endotherm at approximately 270° C. The additional limitations in these disputed terms are not in dispute and simply describe characteristics that the specification associates with Form A. Thus, Natco's construction of Form A applies equally to these terms. Celgene, on the other hand, asserts that no construction is required, in violation of established Federal Circuit precedent mandating that claim construction is required when the disputed terms at issue are technical in nature.[5] *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1476 (Fed. Cir. 1998). Thus, for at least the same reasons discussed above, the Court should adopt Natco's proposed construction.

### D. "Unsolvated Crystalline [lenalidomide]" Terms In Dispute

Certain disputed terms of the Polymorph Patents recite "unsolvated crystalline [lenalidomide]." These terms differ from the "Form A" terms in that they do not expressly use the "Form A" label, but instead, describe lenalidomide in terms of specific physical characteristics such as XRPD, DSC, and/or TGA. Regardless, the specification clearly equates these claimed characteristics with the Form A crystal, to the exclusion of other disclosed crystalline forms. The terms and the parties' constructions are set forth below.

[5] Incredibly, Celgene asserts through its proffered construction of "Form A" that whereas "Form A" requires construction when the term is taken in isolation, no construction is required here.

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| Unsolvated crystalline [lenalidomide] having an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2θ<br><br>(*'219 patent, claim 1*) | The lenalidomide crystal form described in the specification as Form A, having all of the characteristics assigned to Form A in the specification | No construction required |
| An unsolvated crystalline form of [lenalidomide] having an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2θ<br><br>(*'598 patent, claim 10*) | See above | No construction required |
| An unsolvated crystalline form of [lenalidomide] having a differential scanning calorimetry thermogram endotherm at approximately 270 °C<br><br>(*'598 patent, claims 1, 17*) | See above | No construction required |
| An unsolvated crystalline form of [lenalidomide] having a differential scanning calorimetry thermogram endotherm at approximately 270 °C and an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5, and 16 degrees 2θ and a thermogravimetric curve indicative of an unsolvated material<br><br>(*'598 patent, claim 5*) | See above | No construction required |

**1. "Unsolvated crystalline [lenalidomide] having an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2θ"[6]**

This disputed term appears in certain asserted claims of the '219 patent and should be construed to cover Form A lenalidomide. Not only is this construction consistent with the intrinsic record, but it also avoids enablement and written description issues that would arise if Celgene's construction is favored. *See Modine Mfg. Co.*, 75 F.3d at 1557 ("When claims are amenable to more than one construction, they should when reasonably possible be interpreted so as to preserve their validity.") (internal citations omitted).

**a. Natco's Construction Is Consistent With the Specification**

The only unsolvated crystalline lenalidomide described as having an XRPD pattern with peaks at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2θ is the Form A polymorph. (Ex. X, '219 patent, col.6, ll.29-32, Fig. 1.) However, Form A is not only described by its XRPD peaks, but instead, is *also* specifically described as having other characteristics as measured by means including DSC, TGA, IR, and Raman. (Ex. X, '219 patent, col.6, ll.23-64, Figs. 1-5.) Thus, a POSA reading the claim term in the context of the specification would readily recognize that unsolvated crystalline lenalidomide having the claimed XRPD peaks can refer only to Form A lenalidomide having all the attributes assigned to it by the specification.

The *Abbott* case also requires adopting Natco's construction for at least two reasons. *See* 566 F.3d 1282. First, Form A is the only unsolvated crystalline lenalidomide polymorph disclosed and described in the specification as having the seven specifically recited XRPD peaks. (Ex. X, '219 patent, col.6, ll.30-32.) Second, the specification does not teach or even suggest the

[6] These arguments apply equally in support of Natco's construction of the similar term "an unsolvated crystalline form of [lenalidomide] having an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2θ," which appears in certain claims of the '598 patent.

possibility that other unsolvated crystalline polymorphs of lenalidomide exist, let alone having the specifically recited XRPD peaks required by the disputed term.

**b. Celgene Repeatedly Identified "Form A" Disclosures As Enabling And Describing "Unsolvated Crystalline [lenalidomide]"**

During prosecution of the '219 patent, the examiner rejected claims directed to "crystalline [lenalidomide]" having XRPD peaks at 8, 14.5, 16, 17.5, 24, and 26 degrees 2θ for lack of enablement and written description under 35 U.S.C. § 112. In particular, the examiner stated that "[i]f the claims are intended to include other then [sic] exclusively form A of crystalline [lenalidomide] then a 112 first paragraph issue must be raised because . . . none of the other forms have all the characteristics of form A or the dissolution characteristics…." (Ex. Y, '219 patent file history, 12/12/11 Office Action at 3.)

To overcome these rejections, Celgene limited the claims to "unsolvated" crystalline lenalidomide having the seven claimed XRPD peaks, consistent with the specification disclosure of Form A. (Ex. X, '219 patent, col.5, ll.47-48; Ex. Z, '219 patent file history, 3/12/12 Amendment at 2 (see claim 38).) Celgene argued that, "[i]n view of the claim language, a person of ordinary skill in the art would understand that Form H as described in the specification is distinguishable from the instantly claimed subject matter." (Ex. Z, '219 patent file history, 3/12/12 Amendment at 9.) Celgene further argued that "the specification provides many exemplary embodiments, including actual examples, and teaches a POSA how to make and use the claimed subject matter…." (*Id.* at 7-8.) However, the only disclosure in the specification about how to make any "unsolvated" crystalline form of lenalidomide having the seven claimed XRPD peaks is directed to Form A having all the characteristics assigned to it by the specification including XRPD pattern, DSC graph, TGA curve, infrared and Raman spectra, and moisture sorption and desorption data. To the extent they even exist, the specification contains

no disclosure whatsoever about how to make other unsolvated crystalline lenalidomide forms containing those same seven peaks.

Similarly, during prosecution of the '598 patent, Celgene identified specification disclosures pertaining solely to the Form A crystal in arguing that claims directed to "unsolvated crystalline [lenalidomide]" were enabled and sufficiently described. In particular, certain rejected claims were directed to "unsolvated crystalline [lenalidomide]" having an endotherm at "approximately 270 °C" and/or XRPD peaks corresponding to Form A. (Ex. U, '598 patent file history, 6/14/12 Office Action at 2-10; Ex. V, '598 patent file history, 12/12/12 Amendment at 2-5 (see claims 33, 38, and 45).) In response, Celgene identified disclosures in the original application that exclusively describe the characteristics of Form A (*e.g.* XRPD, IR and Raman spectra, DSC and TGA data) as enabling and sufficiently describing the claims. (Ex. V, '598 patent file history, 12/12/12 Amendment at 7, 13.)

Given Celgene's statements and claim amendments during prosecution, a POSA would understand that Celgene intended to claim only the Form A crystal as defined by the various analytical characteristics attributed to it by the specification, and not any other disclosed form.

**2. "An unsolvated crystalline form of [lenalidomide] having a differential scanning calorimetry thermogram endotherm at approximately 270 °C"**

This term appears in certain asserted claims of the '598 patent and should be construed to cover Form A lenalidomide as described by the specification, at least for the reasons discussed in the section above. The claim term recites the characteristics of Form A lenalidomide, but does not expressly use the "Form A" label. Regardless, the term should be construed, as Natco proposes, to cover the Form A crystal as described in the specification because the patent specification discloses Form A, and only Form A, as an "unsolvated crystalline form" of

lenalidomide having a "differential scanning calorimetry thermogram endotherm at approximately 270 °C." (Ex. W, '598 patent, col.6, ll.60-61, Fig. 4.)

**3. "An unsolvated crystalline form of [lenalidomide] having a differential scanning calorimetry thermogram endotherm at approximately 270 °C and an X-ray powder diffraction pattern comprising peaks at approximately 8, 14.5, and 16 degrees 2θ and a thermogravimetric curve indicative of an unsolvated material"**

This term also appears in certain asserted claims of the '598 patent and should be construed to mean Form A lenalidomide having all the characteristics attributed to this form by the specification, at least for the reasons discussed above. The patent specification discloses Form A, and only Form A, as having the specific combination of claimed DSC, TGA, and XRPD characteristics required by the claim term. (Ex. W, '598 patent, col.6, ll.30-32, 60-61, Figs. 1 and 4.) By contrast, the specification does not disclose or even suggest the *possibility* that other crystalline forms, let alone unsolvated crystalline forms, of lenalidomide having the claimed combination of analytical characteristics exist, let alone enable or sufficiently describe any such crystalline form. Accordingly, the Court should adopt Natco's proposed construction as consistent with the specification and file history.

## IV. DISPUTED TERMS OF THE PHARMACEUTICAL PATENTS

U.S. Patent Nos. 6,281,230 (the "'230 patent"), 6,555,554 (the "'554 patent"), and 8,228,415 (the "'415 patent") (collectively the "Pharmaceutical Patents") contain claims directed to lenalidomide, pharmaceutical compositions containing it, and methods of treating various conditions with it.

### A. "Said Compound has the R-Configuration" and "Said Compound has the S-Configuration"

These disputed terms deals with "enantiomers" of lenalidomide, specifically the "R-configuration and S-configuration" of lenalidomide. The parties' proposed constructions are:

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| Said compound has the R-configuration<br><br>(*'230 patent, claim 15; '554 patent, claims 2, 14*) | The stereochemical configuration of the compound is all or substantially all the R-isomer, thus excluding a compound that is a racemic mixture | Said compound has the R-isomer |
| Said compound has the S-configuration<br><br>(*'230 patent, claim 16; '554 patent, claims 3, 15*) | The stereochemical configuration of the compound is all or substantially all the S-isomer, thus excluding a compound that is a racemic mixture | Said compound has the S-isomer |

Natco's construction adheres to established scientific principles and limits the claims to non-racemic forms of lenalidomide that have all or substantially all of either the "R" or "S" enantiomers. The Natco products do not infringe claims with these limitations because it is a racemic form of the compound. Celgene's construction, on the other hand, improperly reads claim terms expressly referring to only one enantiomer as covering the racemic form as well.

**1. Technical Principles**

The claim terms' reference to "R-configuration" and "S-configuration" is a reference to different "enantiomers" of the lenalidomide molecule. (Second Decl. of Robert K. Boeckman, Jr., Ph.D. ("Boeckman Decl.") ¶ 16.) Enantiomers are different versions of the molecule that have the same chemical formula and structural formula, but differ in the three-dimensional orientation of their atoms in space.[7] (*Id.*) These enantiomers are often described as molecules that are non-superimposable mirror images of each other. (*Id.*) One way to think of them is to compare one's left and right hands—each hand is a mirror image of the other and both have

[7] Polymorphs, discussed above, also have identical chemical formulas but have different crystalline structures.

identical components, but they do not overlay in three dimensions, *i.e.*, they do not match up point-for-point when placed over each other. (*See id.*)

When a given compound is made up of equal amounts of the "R" and "S" isomers, it is said to be a "racemic mixture," or a "racemate." (*Id.* ¶ 17.) Because racemic mixtures have equal amounts of the R-isomer and the S-isomer, they are not denoted as having or being in either the "R-" or "S-configuration," and are instead referred to simply by the chemical name of the compound (*e.g.*, lenalidomide). (*Id.* ¶ 18.) Alternatively, racemic mixtures can be denoted by the identifier "(R/S)" or "(+/-)" followed by the chemical name of the compound. (*Id.*) But in no event are racemic mixtures denoted as having the "R-configuration," or the "S-configuration." (*Id.* ¶ 19.) Only when the racemate is separated into individual enantiomers is each separate enantiomer referred to as having either the "R" or "S" configuration. (*Id.* ¶ 19.)

When a compound is referred to as "ha[ving] the R-configuration," a POSA would understand this term to mean that the compound is comprised of all or substantially all the R-enantiomer. (*Id.* ¶ 20.) The S-enantiomer, if present at all, exists as an impurity and is necessarily present in an amount less than 50%. (*Id.* ¶ 22.) Similarly, a POSA would understand that a compound "ha[ving] the S-configuration" means that the compound is comprised of all or substantially all the S-isomer, with any R-isomer occurring as an impurity. (*Id.* ¶¶ 20, 22.) Therefore, consistent with a POSA's understanding, the term "said compound has the R-configuration" means just that: an enantiomer having the R-configuration. This does not include enantiomers having the S-configuration, except as an impurity, and thereby necessarily excludes racemic mixtures (having 50% R-isomer and 50% S-isomer). (*Id.* ¶¶ 20, 22.) Likewise, "said compound has the S-configuration" means an enantiomer having the S-configuration and excluding the racemic mixture. (*Id.* ¶ 20.)

**2. Natco's Construction Is Consistent With The Intrinsic Record**

Natco's proposed construction adheres to these principles and limits the claims to non-racemic forms of lenalidomide that have all or substantially all of either the "R" or "S" enantiomers. This construction is supported by the claims themselves. First, by expressly requiring that the compound being administered "has the R-configuration" (Claims 15 and 24 of the '230 patent), and in other embodiments, "has the S-configuration" (Claims 16 and 25), these claims focus a POSA on the particular enantiomer, not the racemic mixture. (Boeckman Decl. ¶ 20.) By contrast, the broader claims from which claims 15, 16, 24 and 25 depend are directed to the compound without reference to its stereochemical configuration. (*See, e.g.*, Ex. AA, '230 patent at claims 1, 2, 18 and 19; Boeckman Decl. ¶ 20.) Thus, when the claims are intended to cover a particular enantiomer, that enantiomer is expressly recited. When the claims seek to cover the racemic mixture, neither enantiomer is mentioned. (Boeckman Decl. ¶ 21.)

Celgene's construction is inconsistent with this claim language and violates established rules of claim construction. Under the doctrine of claim differentiation, each patent claim is presumptively different in scope because of "the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope." *Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999). Only Natco's proposal can be correct when this principle is applied to the claims at issue. As an example, claim 2 of the '230 patent says nothing about which isomers the compound contains, and it therefore covers the racemic mixture. From a technical standpoint, that racemic mixture contains both the "R" and "S" enantiomers in equal amounts. (Ex. AA, '230 patent at claim 2.) But the only difference between that claim and claims 15 and 16 is that the latter two claims expressly recite that the compound has the "R-" or "S-configuration." (*Id.* at claims 15, 16.) Thus, if these claim terms were to be construed as Celgene suggests, there would be no

difference in scope because claim 2 covers the racemate and, as such, *already* contains equal amounts of the R and S enantiomers.

The specification also makes a clear distinction between racemic mixtures and individual enantiomers having the R- or S- configurations: "Both the racemates of these isomers [i.e., the equal mixture of "R" and "S" lenalidomide enantiomers] and the individual isomers themselves . . . are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers . . . ." (Ex. AA, '230 patent, col.8, ll.2-7.) Thus, the specification teaches that certain embodiments of the invention require the racemate, and other embodiments require having either the *separated* R- or S- enantiomer. That teaching is directly reflected in the claim language as discussed above.

Celgene's statements during prosecution further establish that claims directed to compounds having the R-configuration or the S-configuration were intended to cover use of those isomers alone. For example, during prosecution of the '230 patent, Celgene responded to an Office Action by adding claims directed to each individual enantiomer, further clarifying that in addition to use of the chiral compound, the invention contemplated use of *each individual enantiomer*: "[N]ew claims 67 and 71 are directed to the use of the R-isomer while claims 68 and 72 are directed to the use of the S-isomer, it being disclosed on page 11 that the compounds of the invention possess a center of chirality and can exist as optical isomers." (Ex. BB, '230 patent file history, 2/15/01 Amendment at 3.) *See Phillips*, 415 F.3d at 1317 ("[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.").

Finally, case law on this issue also favors Natco's construction. Courts have consistently interpreted claims directed to single enantiomers to exclude the racemic mixture. In *Ortho-McNeil Pharmaceuticals, Inc. v. Mylan Laboratories,* for example, the court construed "[a]n S(-)-pyridobenzoxazine compound" to refer to the levorotatory enantiomer of ofloxacin and excluding racemic ofloxacin. 348 F. Supp. 2d 713, 724 (N.D. W. Va. 2004). Notably, the court stated that:

> [C]hemists skilled in the art regard levorotatory enantiomers as distinct from racemic compounds or the dextrorotatory enantiomer. Additionally, each type of compound has its own unique nomenclature. "S(-)" clearly designates the levorotatory enantiomer in this case. Had the inventor meant to designate the racemic compound, he would have used the designation "(±)" or "RS."

*Id*. The court also declined to incorporate a numerical limit pertaining to optical purity, concluding that an enantiomer in the "(S)-" configuration more than adequately informed a POSA that the racemic mixture was excluded:

> [T]he term "S(-)" clearly and plainly limits the claim language to the levorotatory enantiomer. Those skilled in the art clearly understand the term "S(-)" to affirmatively denote only the levorotatory enantiomer of a racemic compound, and not the racemic compound itself. Furthermore, those skilled in the art clearly understand the terms "RS" or "(±)" to affirmatively denote a racemic compound. The inclusion of "S(-)" in the claim language, coupled with the obvious exclusion of "RS" or "(±)," militates against Mylan's assertion that an additional plain-English purity limitation is necessary to distinguish the patented invention over the prior art racemic ofloxacin.

*Id.* at 726. Similarly, in a 2013 opinion, this Court construed R(+)-N-propargyl-l aminoindan as being "at least substantially pure" with respect to the S-enantiomer, and to include, at most, "small amounts of the other enantiomer." *Teva Neuroscience, Inc. v. Watson Labs., Inc.*, No. 2:10-cv-05078, 2:11-cv-3076, 2013 WL 1595585, at *7 (D.N.J. Apr. 12, 2013). The Court rejected proposed constructions allowing as much as 49% of the S-enantiomeric impurity noting that "a POSA would understand the term R(+) PAI to mean a compound that is substantially

pure, but not one that requires the complete absence of the S (-) enantiomer." *Id.* at *6. Natco's proposal that the terms be construed to require all or substantially all of the specifically claimed isomer and to exclude the racemic mixture is therefore the correct one and should be adopted over Celgene's construction.

**B. "Unit Dosage Form"**

The next term at issue in these patents is "unit dosage form." While the parties agree that this term is defined in the Pharmaceutical Patent specification and that the specification definition should control, the parties disagree about whether the entire definition should be incorporated into the proposed construction (Natco's proposal) or whether the construction should reflect an arbitrarily truncated version of the definition (Celgene's proposal). The parties' constructions are as follows:.

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| Unit dosage form<br><br>(*'415 patent, claims 1-5*) | Physically discrete units suitable as a unitary dosage containing a predetermined quantity of active material calculated to produce the desired therapeutic effect | Physically discrete units suitable as a unitary dosage |

The specification teaches that:

> The compositions preferably are formulated in unit dosage form, ***meaning*** physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient.

(Ex. CC, '415 patent, col.9, ll.18-25 (emphasis added).) Natco's construction includes the full definition of "unit dosage form." Celgene, however, clips off the language "containing a predetermined quantity of active material calculated to produce the desired therapeutic effect."

Clearly, however, a POSA would understand the disclosure to ***mean*** that the compositions can be formulated as a unit dosage form in association with a pharmaceutically suitable excipient. According to the specification, "each unit contain[s] a predetermined quantity of active material calculated to produce the desired therapeutic effect." Alternatively, the composition can be formulated as a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen. Celgene provides no basis for truncating the definition of this term as clearly set forth in the specification and therefore Natco's construction should govern.

## V. THE REMAINING DISPUTED TERMS

The remaining disputed terms are directed to the dosing regimen—in particular, a "cyclical administration" regimen—and occur in certain asserted claims of the '740 and '569 patents.[8] While these patents do not share the same specification, the disputed issues are similar and should be construed similarly.

Whereas Natco proposes a construction for "cyclical administration" that is consistent with the intrinsic record, and the context of the disclosed and claimed administrations, Celgene asserts that the terms do not need construction. Natco agrees that, in isolation, each word of the disputed phrases is a simple English word whose meaning would be clear to the reader. When read in its entirety, however, the phrase reflects a technical term whose meaning is entirely dependent on context. Indeed, the extrinsic evidence cited by Celgene in support of its non-construction clearly proves this point by providing as many as nine different definitions of "cycle" depending on the biological context. (*See, e.g.*, Ex. DD, Stedman's Medical Dictionary 442-44 (27th ed. 2000); Ex. EE, Taber's Cyclopedic Medical Dictionary 518-20 (19th ed.

[8] The '569 patent, contains claims directed to treating multiple myeloma with a combination therapy of lenalidomide and dexamethasone. The '740 patent claims a method of treating myelodysplastic syndrome ("MDS").

2001).) In this instance, Federal Circuit precedent is clear that when the disputed term is a term of art, rather than a common English term, claim construction is required. *Multiform Dessicants*, 133 F.3d at 1476. Accordingly, Natco's proposals should be adopted.

**A. "Administered in a cycle" / "administered cyclically"**

Both terms occur in certain asserted claims of the '740 patent that require cyclical administration of lenalidomide in treating MDS. The parties' construction are as follows:

| Claim Term | Defendants' Proposal | Celgene's Proposal |
|---|---|---|
| Administered cyclically<br><br>(*'740 patent, claim 18*) | Administered according to a pre-determined dosing regimen that includes administering lenalidomide for an initial period, followed by a pre-determined treatment-free interval, and repeating this sequential administration | No construction required |
| Administered in a cycle<br><br>(*'740 patent, claim 29*) | Same as above | No construction required |

Not only is Natco's construction consistent with established scientific principles including the rationale underlying cyclical dosing versus other types of dosing regimens (*e.g.*, continuous dosing), but it is also fully supported by the intrinsic record. For example, a POSA would have known that cyclical administration allows for the administration of compounds, such as lenalidomide, that are associated with dose-related adverse effects, by providing for a rest period during which the body is allowed to recover from administration of the drug. The specification reflects this rationale, stating that one of the purposes of the claimed cycling therapy is to "reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve[] the efficacy of the treatment." (Ex. FF, '740 patent, col.28, ll.52-55.) A POSA would readily recognize that these beneficial

effects result directly from administering the drug for a period of time, followed by a treatment-free interval, *i.e.*, a rest period, and repeating this sequential administration.

Consistent with this rationale, all cyclical dosing regimens disclosed in the specification teach a treatment-free (rest) period. For example, the specification discloses an exemplary administration using cycling therapy which requires, at a minimum, a 1 or 3 week rest period:

> One cycle can comprise the administration of a therapeutic or prophylactic agent and ***at least one (1) or three (3) weeks of rest.*** The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

(*Id.* at col.28, ll.62-67, col.19, ll.16-21 (emphasis added).) Similarly, the clinical study disclosed in the patent under the section specifically titled "Cycling Therapy in MDS Patients" provides for a pre-determined 7-day rest period following an initial treatment period:

> Patients receive the compound in an amount of 10 mg/d or 15 mg/d for 21 days every 28 days in 4-week cycles for 16 weeks (4 cycles) or 24 weeks (6 cycles).

(*Id.* at col.29, ll.6-8 (Example 2).) In addition, the plain language of the claims requiring cyclical administration themselves specifically incorporate the concept of a rest period. (*Id.* at claims 20, 22, and 30.)

By contrast, where the specification discloses dosing regimens *other than cyclical administration* (for example, continuous administration), it does not teach or suggest a treatment-free interval or rest period. For example, the specification discloses that "[lenalidomide] is administered in an amount of from about 0.1 to about 25 mg per day to patients with MDS for 16 weeks, who are subsequently evaluated for a hematological response." (*Id.* at col.26, ll.51-56.) Additionally, the specification discloses a clinical study in MDS patients wherein "[p]atients received continuous treatment with [lenalidomide] at an oral dose of 25 mg daily." (*Id.* at col.27,

ll.15-17.) In the expanded, related clinical study, patients were administered either 25 mg or 10 mg daily. (*Id.* at col.28, ll.12-15.)

The portions of the specification that Celgene cites in support of its non-construction either do not address cyclic administration at all, and therefore are irrelevant, or support Natco's construction instead. (*See id.* at col.19, ll.4-21 ("In a particular embodiment, prophylactic or therapeutic agents are administered in a cycle of about 16 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic or prophylactic agent *and at least one (1) or three (30 weeks of rest*)." (emphasis added); *id.* at claims 18, 20, 22, and 30.)

To the extent extrinsic evidence is even relevant, given the unambiguous specification definition of these terms, the dictionary definitions Celgene cites are entirely consistent with Natco's proffered construction. Indeed, both cited references require a recurrent sequence occurring at regular intervals, which is consistent with Natco's proposed construction requiring repeated, sequential administration over a pre-determined period. (*See* Ex. DD, Stedman's Medical Dictionary at 442-44; Ex. EE, Taber's Cyclopedic Medical Dictionary at 518, 520.)

**B. "Cyclically administering"**

This term appears in certain asserted claims of the '569 patent, which are directed to "cyclically administering" lenalidomide and dexamethasone in treating multiple myeloma.

| Claim Term | Natco's Proposal | Celgene's Proposal |
|---|---|---|
| Cyclically administering<br><br>(*'569 patent, claim 1*) | Administering lenalidomide and dexamethasone in combination for 21 consecutive days | No construction required |

**1. Natco's Construction Is Consistent With The Specification**

The '569 patent specification devotes an entire section to "Cycling Therapy" in the treatment of multiple myeloma, consisting of administering an immunomodulatory agent (*e.g.*,

lenalidomide) with a second active agent, followed by a period of rest, and repeating this sequential administration. (Ex. GG, '569 patent, col.24, l.20 – col.25, l.9.) In this regard, the specification clearly teaches that the lenalidomide is co-administered with the second active ingredient unless stated otherwise:

> In one embodiment of the invention, an immunomodulatory compound of the invention and a second active ingredient are administered orally, ***with administration of an immunomodulatory compound of the invention occurring 30 to 60 minutes prior to a second active ingredient***, during a cycle of four to six weeks. In another embodiment of the invention, the ***combination of an immunomodulatory compound of the invention and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle***.

(*Id.* at col.24, ll.55-63 (emphasis added).) The specification teaches another exemplary administration in which lenalidomide is administered together with a second active ingredient:

> In a specific embodiment, ***one cycle comprises the administration of from about 10 to about 25 mg/day of REVLIMID$^{TM}$ and from about 50 to about 200 mg/m$^2$/day of a second active ingredient daily*** for three to four weeks and then one or two weeks of rest.

(*Id.* at col.24, l.64 – col.25, l.1 (emphasis added).) However, in instances where the second active ingredient (*e.g.*, dexamethasone) is not co-administered with the immunomodulatory agent over the entire treatment interval, the specification enumerates specific days of the cycle on which the second active ingredient is administered:

> Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination of melphalan (50 mg intravenously), an immunomodulatory compound of the invention (about 1 to 150 mg orally daily), ***and dexamethasone (40 mg/day orally on days 1 to 4)*** every four to six weeks.

(*Id.* at col.38, ll.41-48 (emphasis added).) Therefore, a POSA reading the specification would understand that lenalidomide is co-administered with dexamethasone over the entire treatment interval, except in instances where the specification clearly states otherwise.

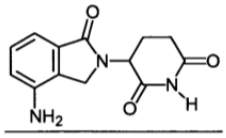
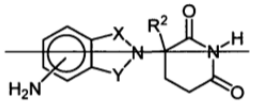
The '569 patent claims also clearly distinguish between administration of lenalidomide and dexamethasone over the entire treatment interval and a regimen where the dexamethasone is only administered on specific days. Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims. *See Rexnord Corp.*, 274 F.3d at 1342; *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1159 (Fed. Cir. 1997). Differences among claims can also be a useful guide in understanding the meaning of particular claim terms. *See Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991). In the present case, claim 13 clearly specifies that the dexamethasone is to be administered on days 1 to 4 of the treatment interval:

> 13. A method of treating multiple myeloma, which comprises administering, on a 28 day cycle, to a patient having multiple myeloma: (a) about 25 mg per day of [lenalidomide] or a pharmaceutically acceptable salt thereof, for 21 consecutive days followed by seven consecutive days of rest from administration of said compound, and; (b) ***40 mg per day of dexamethasone on days 1-4 every 28 days***.

(Ex. GG, '569 patent, col.40, ll.7-25 (emphasis added).) By contrast, claim 1 recites that dexamethasone is to be administered "in combination" with lenalidomide, but does not recite specific days of the treatment interval during which dexamethasone is to be administered. Likewise, none of claims 2-12 that depend from claim 1, recite administering dexamethasone on a certain subset of days within the cycle. Accordingly, a POSA would understand claim 1, and claims depending from claim 1, to require that the lenalidomide is administered in combination with dexamethasone for 21 consecutive days as claimed.

**2. Celgene's Conduct During Prosecution Unequivocally Supports Natco's Proposed Construction**

The prosecution history further confirms that Natco's construction is the correct one. Although Celgene originally pursued claims of similar scope to claim 1 and that clearly required administering dexamethasone on specific days of the cycle, Celgene affirmatively deleted this limitation in favor of language generally reciting that the dexamethasone is administered "during said 28-day cycle." At the same time, Celgene separately pursued, within the same application, claim coverage for administration where the dexamethasone was administered on specific days of the cycle. In particular, Celgene added claim 70, which depended from claim 24, which ultimately issued as claim 1 of the '569 patent. Claims 24 and 70 are reproduced below:

> 24. (currently amended) A method of treating multiple myeloma, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula ~~(I)~~:
>
> 
>
> 
>
> ~~(I)~~
>
> Or a pharmaceutically acceptable salt, solvate or stereoisomer thereof~~, wherein one of X and Y is C=O or $CH_2$ and $R^2$ is hydrogen or lower alkyl~~.
>
> 70. (new) The method of claim 24, wherein the compound is administered in an amount of about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

(Ex. HH, '569 patent file history, 10/28/05 Response at 4, 7.) In a December 7, 2010 response, however, Celgene cancelled claim 70 and amended claim 24 to recite that lenalidomide was administered "for 21 consecutive das followed by 7 days of rest during a 28 day cycle and

cyclically administered about 40 mg of dexamethasone during said 28-day cycle." (Ex. II, '569 patent file history, 12/7/10 Response at 2.) Notably, the limitation that dexamethasone be administered on days 1-4 was not included in amended claim 24. (*Id.*) At the same time however, Celgene continued to maintain coverage of claim scope directed at administering dexamethasone on specific days of the cycle. (*See, e.g.*, *id.* at 3 (Claim 75).) A POSA would understand Celgene's cancellation of language imposing a requirement for dexamethasone administration on specific days of the cycle to mean that dexamethasone can be administered in combination with lenalidomide for 21 consecutive days.

The portions of the specification that Celgene cites in support of its non-construction either do not address cyclic administration at all, and therefore are irrelevant, or support Natco's construction instead. (*See* Ex. GG, '569 patent, col.24, l.19 – col.25, l.9; *id.* at claims 1-15.) Celgene's resort to extrinsic evidence is similarly unavailing because while extrinsic evidence may be considered in determining the meaning of a claim term, "it is less significant than the intrinsic evidence in determining the legally operative meaning of claim language." *Phillips*, 415 F.3d at 1317. This is especially the case where, as here, the inquiry is heavily dependent on the context of the intrinsic record as discussed above. By contrast, the extrinsic evidence Celgene cites generally provides definitions of "cycle" and "cyclic" in a variety of contexts, none of which pertain to dosing regimens. These references are therefore irrelevant. *See Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1332 (Fed. Cir. 1999) ("When the intrinsic evidence is unambiguous, it is improper for the court to rely on extrinsic evidence."). Additionally, where the patentee "acting as his own lexicographer, has clearly set forth a definition of the term," in the specification, that definition should govern. *ACTV*, 346 F.3d at

1091. Therefore, the Court should adopt Natco's proposed construction that aligns itself with the definition provided by the intrinsic record.

## VI. CONCLUSION

For all of the reasons set forth above, Natco urges the Court to adopt its proposed constructions for each of the disputed claims terms of the patents-in-suit.

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**CERTIFICATION OF SERVICE**

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I certify that the foregoing statements made by me are true. I am aware that if any of the foregoing statements are willfully false, I am subject to punishment.

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Dated: October 21, 2013